

TEST PLAN FOR THIODIPROPIONATES CATEGORY14 December, 2001OVERVIEW

The Thioesters Association hereby submits for review a test plan for a category consisting of three substituted thiodipropionates under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of the panel and its member companies to use existing data on these to adequately fulfill the Screening Information Data Set (SIDS) for environmental fate endpoints, ecotoxicity tests, and human health effects for the three substituted thiodipropionates. The Thioesters Association believes that adequate data exist to fulfill all the requirements of the HPV program without the need for additional testing.

RECEIVED
OPPT MDIC

2001 DEC 20 AM 10:46

Test Plan Matrix for Thiodipropionates

	DLTDP 123-28-4	DTTDP 10595-72-9	DSTDP 693-36-7
PHYSICAL CHEMISTRY			
Molecular Weight	514	543	683
Melting point, °C	40	<25	64-67
Boiling point, °C	519 (est)	542 (est)	658 (est)
Vapor Pressure	6.51e-9 mmHg (est)	2.27e-9 mmHg (est)	8.98e-13 mmHg (est)
Water Solubility	<0.1 mg/L (considered insoluble)	<0.1 mg/L (considered insoluble)	<0.1 mg/L (considered insoluble)
Log K _{ow}	11.79 (est)	12.77 (est)	17.68 (est)
ENVIRONMENTAL FATE			
Biodegradation	Not Readily Biodegradable OECD 301B: 57% (Ready Biodegradability by this method is ≥60%)	RA	Inherently Biodegradable OECD 302C: 60% Not Readily Biodegradable OECD 301B: ~ 15% OECD 301C: ~ 40% OECD 301D: ~0%
Hydrolysis	>2 yr.	> 2 yr.	> 2 yr.
Photodegradability	52.0771 e-12 cm ³ /mol-s 2.465 hours	54.9032 e-12 cm ³ /mol-s 2.338 hours	69.0337 e-12 cm ³ /mol-s 1.859 hours
Transport between Environmental Compartments: (Fugacity Level III Model) Default assumption: 1000 kg/hr released into air, water, and soil.	<ul style="list-style-type: none"> • Air: 0.282% • Water: 7.02% • Soil: 30.4% • Sediment: 62.3% 	<ul style="list-style-type: none"> • Air: 0.271% • Water: 7.03% • Soil: 30.3% • Sediment: 62.4% 	<ul style="list-style-type: none"> • Air: 0.0885% • Water: 3.39% • Soil: 29.1% • Sediment: 67.4%
ECOTOXICITY			
Acute Toxicity to Fish (96hr LC50)	>71 mg/L* (analytically confirmed, nominal concentration was 100 mg/L)	RA	>100 mg/L* (based on nominal concentration)
Acute Toxicity to Aquatic Invertebrates (24hr EC50)	10 mg/L* (based on nominal concentration)	RA	780 mg/L* (based on nominal concentration)
Toxicity to Aquatic Plants (72hr EbC50)	33.9 mg/L# (based on nominal concentration)	RA	60 mg/L# (based on nominal concentration)
TOXICOLOGICAL DATA			
Acute Toxicity (oral)	>2500 mg/kg (rat) >2000 mg/kg (mouse)	>2000 mg/kg (rat)	>2000 mg/kg (rat) >2000 mg/kg (mouse)
Acute Toxicity (dermal)	RA	RA	>2000 mg/kg (rat)
Acute Eye Irritation	None - Mild Eye Irritation (rabbit)	RA	Mild Eye Irritation (rabbit)
Acute Skin Irritation	No evidence of exposure related irritation in HRIPT(human)	RA	None - Mild Skin Irritation (rabbit)
Sensitization	Negative (Guinea Pig) Negative (Human)	RA	Negative (Guinea Pig)

Repeated Dose Toxicity	90-day NOAEL = 350 mg/kg/day; NOEL = 125 mg/kg/day	RA	NOEL = 3% dietary level, 2-year exposure (Equates to ~1125 mg/kg/day (for a 400 g Fisher Rat))
Genetic Toxicity-Mutation	<ul style="list-style-type: none"> Ames test – neg host mediated assay -ambiguous 	RA	Ames test – neg
Genetic Toxicity-Chromosomal Aberrations	<ul style="list-style-type: none"> Micronucleus test – neg In vitro cytogenetics study using human embryonic lung cultures, WI-38 cells - neg 	RA	In vitro cytogenetics using Chinese hamster V79 cells- negative
Toxicity to Reproduction	Results of the 90-day repeat dose study indicated there were no macro or microscopic changes in any of the male or female reproductive organs. Thus suggestive that at the doses tested this material would not be a reproductive toxicant.	RA	RA
Developmental Toxicity	<p>Negative in 4 species</p> <p>Rat: NOAEL Material Toxicity & Teratogenicity = >1600 mg/kg/day</p> <p>Mouse: NOAEL Material Toxicity & Teratogenicity = >1600 mg/kg/day</p> <p>Hamster: NOAEL Material Toxicity & Teratogenicity = >1600 mg/kg/day</p> <p>Rabbit: NOAEL Material Toxicity & Teratogenicity = >1000 mg/kg/day</p>	RA	RA

RA– Chemical is part of a category and data needs will be met by structurally similar chemicals.

* - Due to the poor solubility of the test material in water, test substance and solvent (alkylphenol-polyglycol ether alone or in some cases in addition to tetrahydrofuran) were mixed to improve solubility.

- Due to the poor solubility of the test material in water, an emulsifier was used to achieve a better distribution in the medium. The test substance was added to the medium, homogenized with nonylphenol 10EO5PO.

TABLE OF CONTENTS

1.	Information about the Thioesters Association.....	5
2.	Category Analysis	5
2.1	Identity of Category Members	5
2.2	Background Information on Category Members	5
2.3	Use and Exposure Information.....	7
2.3.1	Manufacture:.....	7
2.3.2	Processing:.....	8
2.3.3	Distribution (Transport):.....	8
2.3.4	Uses:.....	8
2.3.5	Disposal:.....	10
3.	Test Plan.....	11
3.1	Chemical and Physical Properties.....	11
3.1.1	Melting Point	11
3.1.2	Boiling Point	11
3.1.3	Vapor Pressure	12
3.1.4	Octanol/Water Partition Coefficients.....	12
3.1.5	Water Solubility.....	12
3.1.6	Test Plan for Physical Properties	12
3.2	Environmental Fate and Pathways	12
3.2.1	Photodegradation.....	13
3.2.2	Stability in Water	13
3.2.3	Biodegradation.....	13
3.2.4	Fugacity.....	13
3.2.5	Test Plan for Environmental Fate Parameters.....	14
3.3	Ecotoxicity.....	14
3.3.1	Acute Toxicity to Fish.....	15
3.3.2	Acute Toxicity to Aquatic Invertebrates	15
3.3.3	Acute Toxicity to Aquatic Plants.....	15
3.3.4	Test Plan for Ecotoxicity.....	15
3.4	Human Health Data.....	16
3.4.1	Acute Toxicity.....	17
3.4.2	Repeated Dose Toxicity.....	17
3.4.3	Genetic Toxicity.....	17
3.4.4	Reproductive Toxicity.....	18
3.4.5	Developmental Toxicity.....	18
3.4.6	Test Plan for Mammalian Toxicity.....	18
3.5	Conclusion.....	18
4.	References	20
5.	Appendix 1 - Robust Summaries	23

1. Information about the Thioesters Association

The Thioesters Association has voluntarily agreed to provide hazard and exposure information under the U.S. EPA HPV Initiative for three chemicals: Propanoic acid, 3,3'-thiobisdidodecyl ester (DLTDP), Propanoic acid, 3,3'-thiobisditridecyl ester (DTTDP) and Propanoic acid, 3,3'-thiobisdioctadecyl ester (DSTDP). The Thioesters Association consists of the following manufacturers of thiobis, propanoic acid, derivatives:

- Crompton Corporation
- Cytec Industries Inc.
- Hampshire Chemical Corp., a wholly owned subsidiary of
The Dow Chemical Company

This plan identifies existing data of adequate quality for these three chemicals, and outlines the intended testing to be conducted.

2. Category Analysis

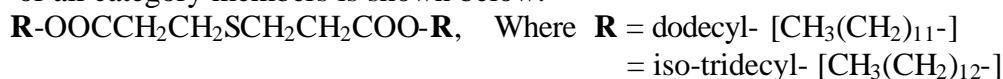
2.1 Identity of Category Members

The substances included in the thiobis, propanoic acid, derivatives category are as follows (listed in order of molecular weight, smallest to largest):

3,3'-Thiobis-, didodecyl ester propanoic acid Dilaurylthiodipropionate (DLTDP)	123-28-4
3,3'-Thiobis-, ditridecyl ester propanoic acid Ditridecylthiodipropionate (DTTDP)	10595-72-9
3,3'-Thiobis-, dioctadecyl ester propanoic acid Distearylthiodipropionate (DSTDP)	693-36-7

2.2 Background Information on Category Members

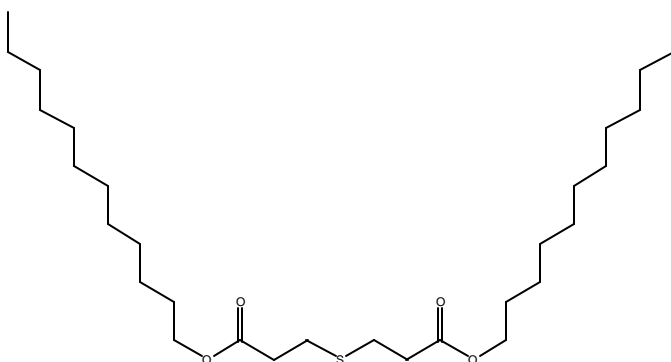
The category consists of three thiobis, propanoic acid di-esters as designated above. The molecular structure of all three category members is essentially the same. The general structure for the category is defined as “3,3’-thiodipropionates.” This describes a molecule with a propanoic ester backbone, in which the functional side chains are extended with aliphatic groups in place of a hydrogen atom. The only structural difference in the three substances is the length of the aliphatic chains. The different aliphatic groups are dodecyl-, iso-tridecyl and octadecyl. The generic molecular structure of all category members is shown below:



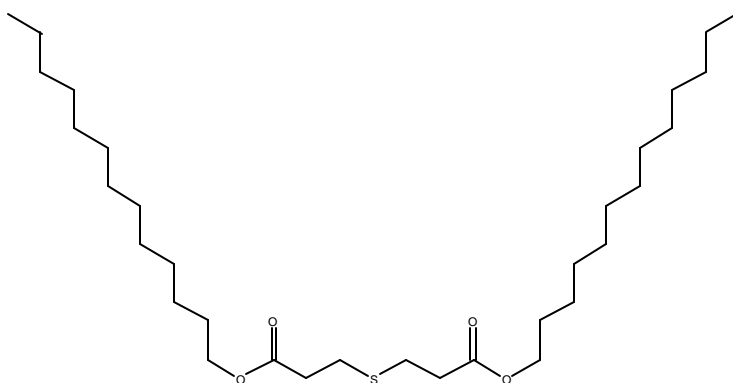
= dioctadecyl- $[(\text{CH}_3(\text{CH}_2)_{17})]$

The three substances are grouped together because of their close structural relationships. In addition, they have similar physiochemical and toxicological properties, further strengthening their familial relationship.

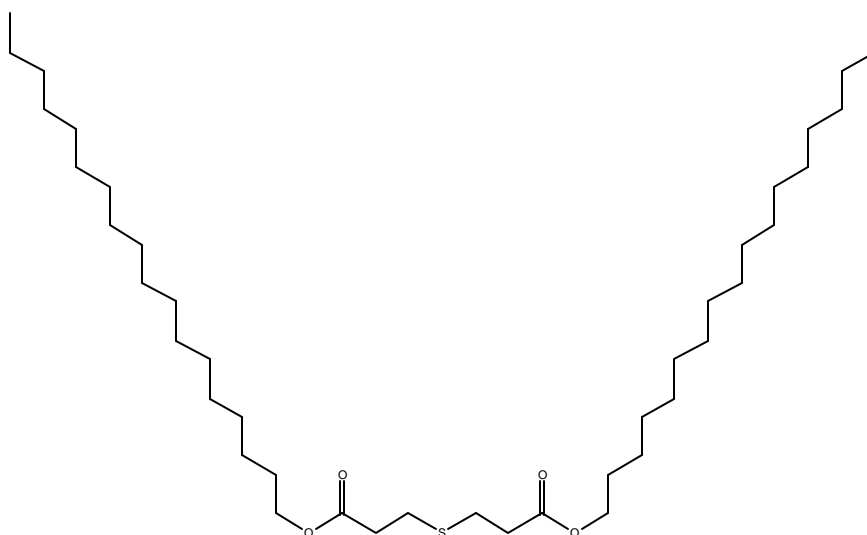
The structures are as follows:



didodecyl 3,3'-thiobispropionate
Dilaurylthiodipropionate, (DLTDP):CAS# 123-28-4



di(tridecyl) 3,3'-thiodipropionate
Ditridecylthiodipropionate (DTTDP): CAS#10595-72-9
(DTTDP contains various n-primary branched alcohol isomers, mainly tridecyl plus other C11-C14 isomers.)



dioctadecyl 3,3'-thiobispropionate
Distearylthiodipropionate (DSTDP): CAS#693-36-7

2.3 Use and Exposure Information

Combined, the manufacturers of DLTPD, DTTDP, and DSTDP produce in excess of 1 million pounds/year of each material. Each manufacturer has prescribed conditions for their manufacture, processing, distribution, use and disposal. In general, there is low potential for exposure of humans or the environment. In the work place, potential worker exposure is carefully controlled.

2.3.1 Manufacture:

DLTPD, DTTDP and DSTDP are all produced by reacting the same intermediate, thiodipropionitrile (TDPN), with different fatty alcohols. DLTPD uses lauryl alcohol, DTTDP uses iso-tridecyl alcohol and DSTDP uses stearyl alcohol. The reaction of TDPN with the alcohols is an esterification using acid catalysts (hydrochloric acid and sulfuric acid). Water is removed under vacuum to drive the esterification to completion. Then the catalyst is neutralized and salts and impurities removed in a series of filtrations and washes. The molten DLTPD and DSTDP are converted to solid products by flaking and packaged. The liquid DTTDP product is drummed.

The TDPN intermediate is made by reacting acrylonitrile and sodium sulfhydrylate in aqueous solution. The resulting aqueous phase is split off, the product phase washed with water and the remaining TDPN used to make the thioesters.

The reactions all take place in enclosed reactors, thus limiting potential worker exposure. The DLTDP, DTTDP and DSTDP all have very low vapor pressures at ambient temperatures so the risk of vapor contact during manufacture and drumming is relatively low.

2.3.2 Processing:

These chemicals are used by our customers who add them to variety of plastics such as polyethylene, polyolefins (mostly polypropylene), and polystyrene. Common use levels of DLTDP and DSTDP are 0.1 to 0.2 %. The polymers are then further processed into items such as washing machine agitators, battery cases, food packaging materials, and household appliances. Additional uses are outlined in Section 2.3.4 Uses.

DLTDP and DSTDP are charged to a feeder from the containers in which they are received by the customer, thus limiting worker exposure. The solid thioesters are transferred by use of a screw conveyor from the feed hopper to an extruder where they are simultaneously melted and mixed with incoming polymer, for example a polyolefin, followed by extrusion of the stabilized polymer.

None of the three thioesters are sold directly to the consumer market. The stabilizers are encapsulated into the polymers in which they are added, limiting potential exposure to the thioesters in the finished consumer products.

2.3.3 Distribution (Transport):

The two solid products are transported to the customers in DOT approved boxes or drums and the liquid thioester in DOT approved drums or bulk tank trucks under established and safe transportation guidelines.

2.3.4 Uses:

All three chemicals are used as secondary antioxidants in a variety of polymer systems including polyolefins, ABS, styrene-butadiene emulsions and certain adhesives. These antioxidants are added to help preserve the integrity of the plastics to which they are added. Common commercial products that may contain low levels of these antioxidants include household appliances such as coffee makers, food packaging trays like those found at the grocers, plastic patio furniture, and plastic covering for wire.

In addition to these uses, DLTDP and DSTDP are FDA approved for use in food-packaging under specific listings in the Code of Federal Regulations (CFR) Title 21-Food and Drugs Chapter I-Food and Drug Administration, Department of Health and Human Services, and DLTDP has both human and animal GRAS applications.

Table 1: 21 CFR Sanctions

21 CFR	Section	Definition
PART 181--PRIOR-SANCTIONED FOOD INGREDIENTS--Table of Contents Subpart B--Specific Prior-Sanctioned Food Ingredients Sec. 181.24 Antioxidants.	§181.24	Substances classified as antioxidants, when migrating from food- packaging material (limit of addition to food, 0.005 percent) shall include: Dilauryl thiodipropionate. Distearyl thiodipropionate.
PART 175--INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS--Table of Contents Subpart C--Substances for Use as Components of Coatings Sec. 175.300 Resinous and polymeric coatings. Sec. 175.380 (Xylene-formaldehyde resins condensed with 4,4'-isopropylidenediphenol-epichlorohydrin epoxy resins.) Sec. 175.390 (Zinc-silicon dioxide matrix coatings)	§175.300 §175.380 §175.390	Resinous and polymeric coatings may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, in accordance with the following prescribed conditions: (b) The coatings are formulated from optional substances that may include: Substances named in this paragraph (b)(3) and further identified as required: (xxx) Antioxidants: Dilauryl thiodipropionate. Distearyl thiodipropionate.
PART 176--INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS--Table of Contents Subpart B--Substances for Use Only as Components of Paper and Paperboard Sec. 176.170 Components of paper and paperboard in contact with aqueous and fatty foods.	§176.170	Substances identified in this section may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods, subject to the provisions of this section.
PART 177--INDIRECT FOOD ADDITIVES: POLYMERS--Table of Contents Subpart B--Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces Sec. 177.1010 Acrylic and modified acrylic plastics, semirigid and rigid.	§177.1010	As antioxidants in the manufacture of semirigid and rigid acrylic and modified acrylic plastics that may be safely used as articles intended for use in contact with food, in accordance with the prescribed conditions. The acrylic and modified acrylic polymers or plastics described in this section also may be safely used as components of articles intended for use in contact with food.
PART 177--INDIRECT FOOD ADDITIVES: POLYMERS--Table of Contents Subpart B--Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces Sec. 177.1200 Cellophane.	§177.1210	Cellophane may be safely used for packaging food in accordance with prescribed conditions.
PART 177--INDIRECT FOOD ADDITIVES: POLYMERS--Table of Contents Subpart B--Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces Sec. 177.1350 Ethylene-vinyl acetate copolymers.	§177.1350	As antioxidants in the manufacture of some ethylene-vinyl acetate copolymers which may be safely used as articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food in accordance with prescribed conditions.
PART 182--SUBSTANCES GENERALLY RECOGNIZED AS SAFE--Table of Contents Subpart D--Chemical Preservatives Sec. 182.3280 Dilauryl thiodipropionate. For use in human food.	§182.3280	Dilauryl thiodipropionate is generally recognized as safe for use in food when the total content of antioxidants is not over 0.02 percent of fat or oil content, including essential (volatile) oil content of the food, provided the substance is used in accordance with good manufacturing practice.

<p>PART 582--SUBSTANCES GENERALLY RECOGNIZED AS SAFE--Table of Contents Subpart D-- Chemical Preservatives Sec. 582.3280 Dilauryl thiodipropionate.</p> <p>For use in animal feed.</p>	<p>§582.3280</p>	<p>Dilauryl thiodipropionate is generally recognized as safe for use in food when the total content of antioxidants is not over 0.02 percent of fat or oil content, including essential (volatile) oil content of the food, provided the substance is used in accordance with good manufacturing or feeding practice.</p>
--	------------------	---

2.3.5 Disposal:

None of the three thioesters are classified as RCRA hazardous wastes.

3. Test Plan

3.1 Chemical and Physical Properties

These materials are structurally similar. DLTDP, DTTDP, and DSTDP have similar physical properties. DLTDP and DSTDP have robust data sets, thus these two materials provide a good bridge among the three materials. Physical property data have been measured, or in some cases, estimated.

Table 2. Chemical/physical properties of substituted thiodipropionates¹

Endpoint	DLTDP 123-28-4	DTTDP 10595-72-9	DSTDP 693-36-7
Molecular formula	C ₃₀ H ₅₈ O ₄ S	C ₃₂ H ₆₂ O ₄ S	C ₄₂ H ₈₂ O ₄ S
Molecular weight	514	543	683
Physical State	White flakes	Liquid	White flakes
Melting point, °C	40	<25	64-67
Boiling point, °C ³	<i>519 (est)</i> ²	<i>542 (est)</i>	<i>658 (est)</i>
Vapor pressure, mmHg @ 25°C	<i>6.51e-9 mmHg (est)</i>	<i>2.27e-9 mmHg (est)</i>	<i>8.98e-13 mmHg (est)</i>
Water Solubility, mg/L @ 25°C	<0.1 (considered insoluble)	<0.1 (considered insoluble)	<0.1 (considered insoluble)
Partition coefficient (Log K _{ow})	<i>11.79 (est)</i>	<i>12.77 (est)</i>	<i>17.68 (est)</i>

Italicized values in Table 2 designate values obtained by EPIWIN

¹Values shown above are for neat substances.

²(est) =Estimated mean value

³Will decompose on heating

3.1.1 Melting Point

The melting point values for the solid materials are consistent with each other. As the side chain increases the melting point increases. DTTDP is a liquid material and would be expected to have a melting point that is lower than room temperature (due to its liquid state at room temperature). The actual value for this material is <25°C.

3.1.2 Boiling Point

The boiling points of all category members in the form of the neat product are not applicable because these materials will degrade when heated above 300°C. However, estimated values calculated by EPIWIN (Syracuse Research Corporation 2000) on the boiling points of these compounds suggests that the boiling points increase with increasing structural substitution (Table 2).

3.1.3 Vapor Pressure

The vapor pressures of all four compounds are negligible. This conclusion is based upon information derived from modeling (Syracuse Research Corporation 2000).

3.1.4 Octanol/Water Partition Coefficients

The log K_{ow} values for the three substituted thiodipropionates have been estimated using the EPIWIN program algorithms (Syracuse Research Corporation 2000). These are 11.79 for the dodecyl-, 12.77 for the tridecyl and 17.68 for the octadecyl esters. The differences in log K_{ow} values correlates roughly with the length of the alkyl chains in the ester function.

3.1.5 Water Solubility

Information on the solubility of these compounds comes from both modeling studies and laboratory experiments. The alkyl side chain substitutions employed to obtain DLTDP, DTTDP, and DSTDP render the compounds practically insoluble (Cytec MSDS ; Hampshire MSDS). The estimated solubility of the three esters in water is < 0.1 g/l at 25° C, virtually insoluble in water.

3.1.6 Test Plan for Physical Properties

Pertinent physical property values have been determined either through measurement or estimations using models, such as EPIWIN. No additional determinations are needed.

3.2 Environmental Fate and Pathways

Results of environmental fate studies with the three substituted thiodipropionates are summarized in Table 3.

Table 3. Environmental fate studies with substituted thiodipropionates

Endpoint	DLTDP 123-28-4	DTTDP 10595-72-9	DSTDP 693-36-7
Biodegradation	Not Readily Biodegradable OECD 301B: 57% in 28 days (Ready Biodegradability by this method is $\geq 60\%$ in 28 days)	RA	Inherently Biodegradable OECD 302C: 60% Not Readily Biodegradable OECD 301B: up to 15% OECD 301C: avg. 40% OECD 301D: 0%
Hydrolysis	>2 years	>2 years	>2 years
Photodegradability	<i>52.0771 e-12 cm³/mol-sec</i>	<i>54.9032 e-12 cm³/mol-sec</i>	<i>69.0337 e-12 cm³/mol-sec</i>

Italicized values are derived from EPIWIN model

3.2.1 Photodegradation

The results of EPIWIN modeling (Table 3) indicate that degradation accelerates with increasing substitution (Syracuse Research Corporation 2000).

3.2.2 Stability in Water

The EPIWIN model predicts that these compounds are stable in water (i.e. resistant to hydrolysis) with half-lives estimated at greater than one year (Table 3).

3.2.3 Biodegradation

Ready biodegradability tests are stringent tests that provide limited opportunity for biodegradation and acclimatization to occur. Thus making it possible to assume that a chemical giving a positive result in a test of this type will rapidly biodegrade in the environment and, therefore, be classified as “readily biodegradable.” However, one should also look to tests for inherent biodegradability before passing judgment as to whether or not a material will biodegrade in the natural environment. In tests for inherent biodegradability prolonged exposure of the test substance to micro-organisms is allowed and provides a more favorable test compound/biomass ratio thus resulting in conditions that favor biodegradation. A compound giving a positive result in a test of this type is typically classified as inherently biodegradable.

Results from OECD Guideline Studies for Ready Biodegradability indicate that DLTPD and DSTPD were both determined not to be readily biodegradable. However rates of biodegradation were scored at 57% for DLTPD and 40% for DSTPD (Ready Biodegradability requires a value of $\geq 60\%$). Using the OECD Guideline Study 302C: Inherent Biodegradability Modified MITI Test (II), biodegradation of DSTPD was determined to be inherent with a biodegradation rate of 60%. In these studies, a figure of more than 20% biodegradation is regarded as evidence for inherent, primary biodegradation and a figure of $>70\%$ may be regarded as evidence for ultimate biodegradation. As DSTPD is a larger molecule than the other members of this category one would expect the inherent biodegradability of both DLTPD and DTTDP to be even greater than that of DSTPD. Additional biodegradation studies are not proposed for these materials. These materials are estimated to be inherently biodegradable based on the data available.

3.2.4 Fugacity

Estimation of relative distribution of a chemical released into various environmental compartments can be estimated using the Mackay Level III fugacity model (Syracuse Research Corporation 2000). This model cannot be employed to predict actual environmental concentrations. One of the key assumptions underlying this model, is the assumption of zero loss of material through degradation or dispersion out of the environmental system. When applied to DLTPD, DTTDP, and DSTPD, the model predicts that all three compounds partition

primarily to sediment and to a slightly lesser degree to soil. Partitioning to water and air is negligible (Table 4). The default assumption conservatively assumes the simultaneous release of 1000 kg/hr to air, water, and soil. Calculations using alternate emission assumptions are presented in the attached robust summaries.

Table 4. MacKay Level III fugacity model

Medium (Emission Rate)	DLTDP 123-28-4	DTTDP 10595-72-9	DSTDP 693-36-7
	Concentration %	Concentration %	Concentration %
Air (1000 kg/hr)	0.282	0.271	0.0885
Water (1000 kg/hr)	7.02	7.03	3.39
Soil (1000 kg/hr)	30.4	30.3	29.1
Sediment (0 kg/hr)	62.3	62.4	67.4

3.2.5 Test Plan for Environmental Fate Parameters

Pertinent environmental fate values for these materials include biodegradation, photodegradation, and fugacity. Adequate values for photodegradation and fugacity have been determined through estimations using EPIWIN. No additional determinations are needed. Biodegradability has been determined for DLTDP and DSTDP according to OECD Guideline Methods. This data will be considered sufficient for read across purposes.

3.3 Ecotoxicity

Results of ecotoxicity studies with the three substituted thiodipropionates are summarized in Table 5.

Table 5. Ecotoxicity Studies with Substituted Thiodipropionates

Endpoint	DLTDP 123-28-4	DTTDP 10595-72-9	DSTDP 693-36-7
Acute toxicity to Fish	96HR LC50 = >71 mg/L (analytically confirmed, nominal concentration = 100 mg/L)	No data	96HR LC50 = >100 mg/L (based on nominal concentration)
Acute toxicity to Daphnia	24hr EC50 = 10 mg/L (based on nominal concentration although concentrations were confirmed analytically)	No data	24hr EC50 = 780 mg/L (based on nominal concentration)
Toxicity to Algae	72Hr EbC50 = 33.9 mg/L (based on nominal concentration)	No data	72Hr EbC50 = 60 mg/L (based on nominal concentration)

3.3.1 Acute Toxicity to Fish

Data are available for DLTDP and DSTDP. No tests are proposed for DTTDP. The information available will be applied as read across data.

It should be noted that no adverse aquatic effects were seen at the highest concentrations tested and that the concentrations tested were well above the water solubility for each material. As such, under natural conditions one would expect the potential aquatic toxicity to fish to be even lower.

3.3.2 Acute Toxicity to Aquatic Invertebrates

Data are available for DLTDP and DSTDP. No tests are proposed for DTTDP. The information available will be applied as read across data.

It should be noted that the concentrations tested were well above the water solubility for each material. As such, under natural conditions one would expect the potential aquatic toxicity to be even lower.

3.3.3 Acute Toxicity to Aquatic Plants

Data are available for DLTDP and DSTDP. No tests are proposed for DTTDP. The information available will be applied as read across data.

It should be noted that the concentrations tested were well above the water solubility for each material. As such, under natural conditions one would expect the potential aquatic toxicity to be even lower.

3.3.4 Test Plan for Ecotoxicity

Ecotoxicity testing is not proposed based on available data for DLTDP and DSTDP. The information available will be applied as read across data.

3.4 Human Health Data

Results of mammalian toxicity tests are summarized in Table 6.

Table 6. Mammalian toxicity of Substituted Thiodipropionates.

Endpoint	DLTDP 123-28-4	DTTDP 10595-72-9	DSTD 693-36-7
Acute Toxicity (oral)	>2500 mg/kg (rat); >2000 mg/kg (mouse)	> 2000 mg/kg (rat)	>2000 mg/kg (rat); >2000 mg/kg (mouse)
<i>Acute Toxicity (dermal)</i>	-	-	>2000 mg/kg (rat)
<i>Acute Eye Irritation</i>	None to Mild Eye Irritation (rabbit)	-	Mild Eye Irritation (rabbit)
<i>Acute Skin Irritation</i>	No evidence of exposure related irritation in HRIPT*(human)	-	None to Mild Skin Irritation (rabbit)
<i>Sensitization</i>	Negative (Guinea Pig) Negative (Human)	-	Negative (Guinea Pig)
Repeated dose	90-day NOAEL = 350 mg/kg/day; NOEL = 125 mg/kg/day	-	NOEL = 3% dietary level, 2-year exposure (Equates to ~1125 mg/kg/day (for a 400 g Fisher Rat))
Genetic toxicity (bacterial mutagenesis)	<ul style="list-style-type: none"> Ames test – Negative Host mediated assay - ambiguous 	-	Ames test – Negative
Genetic toxicity (chromosome aberration)	<ul style="list-style-type: none"> Micronucleus Test – Negative In vitro cytogenetics study using human embryonic lung cultures, WI-38 cells – Negative 	-	Two in vitro cytogenetics assays using Chinese hamster V79 cells - Both negative
Reproductive toxicity	Results of the 90-day repeat dose study indicated there were no macro or microscopic changes in any of the male or female reproductive organs. Thus suggestive that at the doses tested this material would not be a reproductive toxicant.	-	-
Developmental toxicity	Negative in 4 species	-	-

Developmental toxicity	Rat: NOAEL Material Toxicity & Teratogenicity = >1600 mg/kg/day Mouse: NOAEL Material Toxicity & Teratogenicity = >1600 mg/kg/day Hamster: NOAEL Material Toxicity & Teratogenicity = >1600 mg/kg/day Rabbit: NOAEL Material Toxicity & Teratogenicity = >1000 mg/kg/day		
------------------------	--	--	--

*HRIPT = Human Repeat Insult Patch Test

3.4.1 Acute Toxicity

Oral LD₅₀ values have been reported for DLTDP, DTTDP, and DSTDP. These values are consistent with each other and indicate that these materials have a low order of acute oral toxicity.

A dermal LD₅₀ value has been reported for DSTDP. This indicates a low order of acute dermal toxicity.

Acute eye and skin irritation studies have been reported for DLTDP and DSTDP. These values are consistent with each other and indicate that these materials have a low potential to irritate the eyes and skin.

Dermal sensitization studies have been reported for DLTDP and DSTDP. These values are consistent with each other and indicate that these materials are not sensitizing.

3.4.2 Repeated Dose Toxicity

Adequate repeat dose toxicity data exists for DLTDP. DLTDP has the lowest molecular weight in this category thus the toxicity of DTTDP and DSTDP would be expected to be the same or less. As such these results will be bridged to the other members of this category. In addition, data for DSTDP is also available and is supportive of the DLTDP study. No repeated dose toxicity testing is proposed.

3.4.3 Genetic Toxicity

Adequate genetic toxicity data exists for DLTDP and DSTDP. As such these results will be bridged to the other two members. No genetic toxicity testing is proposed.

3.4.4 Reproductive Toxicity

Adequate repeat dose toxicity data with specific evaluation of the reproductive organs exists for DLTPD. As such these results will be bridged to the other members of this category. Since DLTPD has the lowest molecular weight in this category the toxicity of DTTDP and DSTDP would be expected to be the same or less. No reproductive toxicity testing is proposed.

3.4.5 Developmental Toxicity

Adequate developmental toxicity data exists for DLTPD. As such these results will be bridged to the other members of this category. Since DLTPD has the lowest molecular weight in this category the toxicity of DTTDP and DSTDP would be expected to be the same or less. No developmental toxicity testing is proposed.

3.4.6 Test Plan for Mammalian Toxicity

The variety and quantity of the studies available and consistency of the study findings across animal species, test paradigms and members of this class of compounds is more than sufficient to characterize the potential mammalian toxicities of concern. Therefore, no additional testing is being proposed.

3.5 Conclusion

The Thioesters Association has reviewed the available data and prepared a test plan for three substituted Thiodipropionates under the EPA HPV Chemical Challenge Program. These analyses included the evaluation of data related to the SIDS endpoints for environmental fate endpoints, ecotoxicity tests, and human health effects. The existing data evaluated in this analysis included that which is available on each of the three members of this category.

The similarity of these chemicals becomes apparent following a cursory review of their structures. DLTPD, DTTDP, and DSTDP are simply 3,3'-thiodipropionates with increasing aliphatic side chain substitutions.

The overall conclusions of these analyses include:

- 1) there exists a very extensive body of studies available on this family of compounds;
- 2) the physical/chemical and biological characteristics of these compounds are very similar; and
- 3) the use of data from DLTPD and DSTDP to substitute for missing data for DTTDP provides a good estimate of potential toxicity.

These conclusions are supported in part by the following:

- 1) The extensive Physical Chemistry information available demonstrates the similarity of DLTPD, DTTDP, and DSTDP (e.g. boiling points and vapor pressure). The variations observed between these three materials are reflections of increasing chain length.
- 2) Sufficient Environmental Fate information is available for DLTPD and DSTDP. The similarities in these data are obvious (e.g. all compounds are relatively stable in purified water and are not readily biodegradable under test conditions, but are anticipated to all be inherently biodegradable by naturally occurring microorganisms). Potentially the negative environmental impact appears to be greatest with DLTPD because it has the shortest chain length (i.e. photolysis rate increases with increasing chain length). The actual differences among the three are anticipated to be minimal.
- 3) Consistent with predictions based upon Physical Chemistry and Environmental Fate knowledge, DLTPD and DSTDP are relatively similar with regard to Ecotoxicity, except for results for the aquatic invertebrates where shorter chain length demonstrates a role in increasing aquatic toxicity. One should, however, take into consideration that these material are not water soluble and under test conditions solubility was assisted in order to conduct the studies. Under natural conditions one would expect the toxicity to be lower.
- 4) Results of toxicology studies are consistent with the conclusions expressed and supported above (i.e., the compounds are similar, but toxicity is estimated to decrease with increasing chain length). Thus, DLTPD is estimated to have higher toxicity than the other compounds in this family, thus serving as a conservative default for a data source.
- 5) Results of genetic toxicity testing are comparable between DLTPD and DSTDP. These compounds are negative in the Ames assay and negative in tests of chromosomal aberration. This data would be representative across the other member of this chemical family.
- 6) Developmental toxicity testing in DLTPD produced no adverse results in four separate species. Also, in a 90-day repeat dose study with DLTPD, no effects on reproductive organs were observed. Since DLTPD is the smallest of the three materials it is estimated to be an appropriate conservative representative for the family.

These data led the Thioesters Association to conclude that the available data are sufficient to meet the requirements for these Thiodipropionates under the EPA HPV Chemical Challenge Program.

4. References

- AFREAW Advances in Food Research (1951). Academic Press Inc., 1 E. First St., Duluth MN 55802. Vol 3:197.
- Ames (1971). The detection of chemical mutagens with enteric bacteria. Chemical Mutagens: Principles and methods for their detection. Vol 1 Chapter 9:267-282.
- Ames et al., An improved Bacterial Test System for the Detection and Classification of Mutagens and Carcinogens. Proc.Natl.Acad.Sci. USA 70, 782-786
- Ames et al., Carcinogens and Mutagens: A Simple Test Method Combining Liver Homogenates for Activation and Bacteria for Detection. Proc.Natl.Acad.Sci. USA 70, 2281-2285
- Ames et al., Methods for Detecting Carcinogens and Mutagens with the Salmonella/Mammalian-Microsome Mutagenicity Test. Mutation Res. 31, 347-364
- Bar, F. and Griepentrog, F. (1960). Medizin Ernahr 1:100 cited in BIBRA (1989). Didodecyl thiodipropionate.
- Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.
- Ciba Additive GmbH Lampertheim
Ciba Specialty Chemicals Inc. Basel
Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
- Clariant GmbH (1994), EG-Sicherheitsdatenblatt (29.08.94)
- CYTEC MSDS (05/21/99) CYANOX 711 Antioxidant MSDS.
- CYTEC MSDS (9/01/98). CYANOX STDP Antioxidant MSDS.
- CYTEC MSDS (9/01/98). CYANOX LTDP Antioxidant MSDS.
- Dow Chemical Co. MSDS (09/14/99). Ditridecyl thiodipropionate.
- FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropionic acid) NTIS PB-223 824.

Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Hampshire MSDS (09/14/99). Ditridecyl thiodipropionate.

Hampshire MSDS (2000).

Hampshire MSDS (3-31-97). Dilauryl thiodipropionate MSDS.

Hawley, G.G. (1977). The Condensed Chemical Dictionary, 9th ed. New York: Van Nostrand Reinhold Co.

Hoechst AG (1995): EG-Sicherheitsdatenblatt Hostanox SE 4 (19.05.1995)

In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells with TK10594 (Irganox PS802). January 5, 1998

Keeler, P.A. and Olson, K.J. (1975). Toxicological properties and industrial handling hazards of distearyl thiodipropionate. Unpublished report of The Dow Chemical Company.

Lehman A.J., O.G.Fitzhugh, A.A.Nelson, and G.Woodard, Adv. Food Res.,3,197(1951)

Lehman, A.J. et al., (1951). The pharmacological evaluation of antioxidants. Advances in Food Research. 3:197-208.

Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Maibach, H.I., Gellin, G. and Ring, M. (1975). Is the antioxidant butylated hydroxytoluene a depigmenting agent in man? Contact Dermatitis 1:295-296.

Marhold, J. (1972). Sbornik Vysledku Toxikologickeho Vysetreni Latek A Pripravku, p. 174 Cited in NIOSH RTECS 98-3 (August 1998).

P.E.Tullar et al., Pharmaceutical Properties of Thiodipropionic acid, "Dilauryl"thiodipropionate, and "Distearyl"Thiodipropionate. , A Progress Report, The George Washington University, the Kalusowski Memorial Research Laboratory , Washington D.C., School of Pharmacy, November 1, 1947

Pullin, T.G. and Schwebel, R.L. (1974). Acute toxicological properties and industrial handling of ... bis-(tridecylpropionate) thioether. Unpublished Dow Chemical Company report.

Report of a 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basle Switzerland. December 14, 1993.

Report on the Growth Inhibition Test of IRGANOX PS 800 to Green Algae (*Scenedesmus subspicatus*), Ciba-Geigy Ltd. Basle, Switzerland. September 16, 1992.

Report on the Growth Inhibition Test of IRGANOX PS 802 to Green Algae (*Scenedesmus subspicatus*), Ciba-Geigy Ltd. Basle, Switzerland. December 17, 1992.

Report on the Test for Acute Toxicity of IRGANOX PS 802 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. January 9, 1989.

Report on the Test for Acute Toxicity of TK10030 to *Daphnia Magna*, Ciba-Geigy Ltd. Basle, Switzerland. November 25, 1988.

Report on the Test for Acute Toxicity of TK10030 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. December 2, 1988.

Report on the Test for Acute Toxicity of TK10594 to *Daphnia Magna*, Ciba-Geigy Ltd. Basle, Switzerland. December 16, 1988.

Report on the Test for Ready Biodegradability of TK10030 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. February 21, 1989.

Report on the Test for Ready Biodegradability of TK10594 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. April 4, 1989.

Reynolds, R.C. et al., (1974). The fate of 14Cthiodipropionates in rats. *Toxicol Appl Pharmacol* 28:133-141.

Salmonella Mutagenicity Test with Three Strains with TK 10594 (IRGANOX PS 802). Ciba-Geigy Ltd. Basle, Switzerland. June 23, 1989.

SRI International (1979). Microbial mutagenesis testing of substances; compound report: F76-049, dilauryl thiodipropionate. NTIS report PB89169031.

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000)

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

5. Appendix 1 - Robust Summaries



December 11, 2001

Christine Todd-Whitman, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Re: HPV Chemical Challenge Program, Amendment of Commitment on CAS No. 4131742.
EPA Internal Tracking Number AR201-12067

Dear Ms. Whitman:

Crompton Corporation on 22 December 1999 informed you that it was sponsoring CAS No. 4131742 under the HPV Chemical Challenge Program as follows:

CAS Number	Chemical Name	Start Year Date	Consortia/Panel
4131742	Propionic acid, 3,3'-thiobis-, dimethyl ester	2001	Regnet Thioesters Association

Through this letter, we are informing you that Crompton Corporation will transfer its sponsorship of CAS No. 4131742 from the Thioesters Association (under the HPV Program in 2001) to individual chemical status under HPV Challenge Program (with a start date of 2003).

CAS Number	Chemical Name	Start Year Date	Consortia/Panel
4131742	Propionic acid, 3,3'-thiobis-, dimethyl ester	2003	None

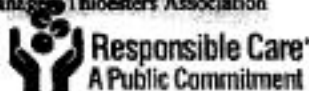
Crompton's commitment for the remaining CAS Nos. listed in our 22 December 1999 letter to you remains intact.

Should you have any questions please do not hesitate to contact me directly at (203) 573-2219. My fax number is (203) 573-4531.

Sincerely yours,

Alan Taylor, Ph.D.
Director, Product Safety and Regulatory Affairs
Crompton Corporation

cc: Barbara Leczynski, USEPA
Larry Rampy, ACC Product Stewardship Team
Jim Keith, ACC Product Stewardship Team
Betty Hunt, Panel Manager, Thioesters Association



Crompton Corporation 199 Sutton Road, Woburn, MA 01801